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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/024,520	12/21/2001	Jacobus M. Lemmens	ADP-019US	2171

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EXAMINER	
PULLIAM, AMY E	
ART UNIT	**PAPER NUMBER**
1615	10

DATE MAILED: 08/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/024,520	Applicant(s) LEMMENS ET AL.	
	Examiner Amy E Pulliam	Art Unit 1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/20/03* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10, 12 and 34-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 12-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Receipt of Papers

Receipt is acknowledged of the Extension of Time and the Amendment B, both received March 20, 2003.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-10, 12, and 35-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 5,155,120 to Lazar *et al.*. Lazar *et al.* disclose a method for the treatment of congestive heart failure using amlodipine and the pharmaceutically acceptable acid addition salts thereof (abstract). More specifically, Lazar *et al.* teach that the generic name amlodipine represents the free base (c 2, l 11-13). Lazar *et al.* also teach that in the treatment of congestive heart failure it is pereferred to administer amlodipine (so the free base) or its pharmaceutically acceptable acid addition salts orally once a day (c 2, l 21-24). Lazar *et al.* also teach that tablets are use for the oral administration of the composition. Lazar *et al.* also teach that inclusion of various well known excipients into the composition, such as dicalcium phosphate.

Lazar *et al.* do not specifically teach the inclusion of anhydrous calcium hydrogen phosphate or microcrystalline cellulose. However it is the position of the examiner that the use

of well known pharmaceutical additives in a tablet formulation does not render patentable weight to the claim.

Additionally, US Patent 4,879,303 to Davison *et al.* is relied upon to further reiterate that the claimed excipients are well known in the art. Davison *et al.* teach pharmaceutical compositions comprising amlodipine. More specifically, Davison *et al.* teach that the invention provides for a tablet formulation comprising a salt of amlodipine mixed with excipients, including microcrystalline cellulose as a compression aid, anhydrous calcium phosphate to provide sheen, sodium starch glycolate as a disintegrant and magnesium stearate as a lubricant (c 1, l 43-51). Although this reference teaches that salt form of the active, rather than the free base, this is umimportant, because the reference is relied upon to show that applicant's well known excipients are known in the tablet art, and are more specifically known in tablets containing applicant's claimed active.

Lazar *et al.* also does not specifically teach that the free base be in form I or form II. However, it is the position of the examiner that one of ordinary skill in the art would consider both form I and form II to fall within the broad teachings of amlodipine free base in general. Absent a showing of criticality in using on form over another, it is the position of the examiner that the teachings of Lazar *et al.* suggest both forms of the free base. Applicant is encouraged to submit any data showing unexpected results in using one form of the free base over another. Lastly, the reference does not specifically teach the residue on the tablet punch. However, there is no teaching in the reference which states that the value is different than the value claimed by applicant. The burden is shifted to applicant to show any differences in this value. The Office does not have the facilities for examining and comparing applicant's product with the product of

the prior art in order to establish that the product of the prior art does not possess the same material structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. *See Ex parte Phillips*, 28 U.S.P.Q.2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), *Ex parte Gray*, 10 USPQ2d 1922, 1923 (PTO Bd. Pat. App. & Int.) and *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Furthermore, the criticality of the base form alone is not clear to the examiner. More specifically, the dependant claims recite dicalcium hydrogen phosphate as an additive, and the specification, at page 11, lines 17-22, teaches that the tablet formulation can be made through wet granulation. In this process, the free base would react with the phosphate ions in solution, and create a salt. This is also true for the crystalline form of the active. If the tablet is made through wet granulation, which is specifically disclosed in the specification, the active will form a salt, and the criticality of the crystalline form then becomes unclear. Therefore, clarification on these two points is requested.

Lastly, Lazar *et al.* do not teach that the active agent be in particle form and be a particular particle size. However, it is the position of the examiner that it is well known in the art of tablet making (wet granulation, dry granulation, and direct compression) that the active agent be present in particulate form. Furthermore, it is the position of the examiner that absent a showing of criticality, the determination of a particular particle size is within the skill of the ordinary worker as part of the process of normal optimization.

Therefore, it is the position of the examiner that based on the teachings of Lazar *et al.*, (that the generic name of amlodipine refers to the free base of the active agent), and the additional teachings to tablets, excipients, and method of use, applicant's pending claims are rendered obvious over the reference. One of ordinary skill in the art would have been motivated to use well known tablet excipients in a tablet formulation with the expectation of success. Therefore, this invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments filed have been fully considered but they are not persuasive. Applicant has amended the claims to include that the amlodipine free base is selected from the group consisting of crystalline Form I, crystalline Form II, and mixtures thereof. Applicant argues that Davison teaches away from the claimed invention, because Davison teaches that the free base is known to be sticky. However, this point is moot, ads the pending claims no longer recite the "low punch residue" limitation. However, even if this limitation is reinserted into the claims, it is recommended that Applicant provide a side by side comparison, showing that the prior art free base differs from the instantly claimed free base.

Applicant argues that Lazar fails to teach or suggest the formation of crystalline amlodipine free base, or the formation of Form I or Form II. Applicant restates the argument with respect to the Davison reference. The examiner does not find this argument to be persuasive for several reasons.

First, Applicant has repeatedly stated that the unexpected result found with their invention is a free base with low punch residue, therefore making it successful in tablet formulation. Now, Applicant has amended the claim to recite that the free base is crystalline. However, upon careful examination of the specification, the examiner finds that Applicant has shown no criticality in the use of the crystalline form over the amorphous form of the free base. For example, on page 5 of the specification, Applicant states, "the amlodipine free base can be of any form including crystalline form I, crystalline form II, or amorphous." Therefore, Applicant himself has admitted that there is no criticality in using the crystalline or the amorphous form

Second, Applicant has not clearly shown that the prior art does not use the crystalline form. Applicant has submitted a reference which discusses the benefits of the crystalline form. However, this does not explicitly exclude the possibility that the cited prior art used the crystalline form. However, based on the above discussion, even if the prior art used the amorphous form, Applicant himself states that any of the forms can be used.

The references teach that amlodipine free base is known. The references contain no discussion of amorphous versus crystalline forms of the free base. However, Applicant himself discloses that any of the three can be used in their invention. This discussion leads one to believe that any success Applicant is achieving in tableting the free base is not a result of the crystalline form of the drug. Lastly, the examiner observes that Applicant has provided no data showing the criticality of the crystalline forms versus the amorphous form. Any such data should be provided in declaration form. For the above reasons, the rejection is maintained and made final.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E Pulliam whose telephone number is 703-308-4710. The examiner can normally be reached on Mon-Thurs 7:30-5:00, Alternate Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on 703-308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3592 for regular communications and 703-305-3592 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
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